Detection of Glaucomatous Progression

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INTRODUCTION

Glaucoma is a progressive optic neuropathy identified by characteristic optic disc, retinal nerve fiber layer (RNFL) and visual field damage and change that occur as a result of retinal ganglion cell damage and death. Detecting structural and functional change is one of the most challenging aspects of glaucoma management.¹⁻⁴ Detecting progression requires detailed documentation of the appearance of the optic disc and visual field at each visit so that change over time can be identified. In the clinical setting, structural change is usually identified based on a thorough clinical examination, with a drawing or written description of the optic disc and retinal nerve fiber layer often augmented with subjective assessment of optic disc photographs to summarize the examination results. Automated perimetry provides objective documentation of visual function that can be used to compare visual fields over time.

Fortunately, objective tools to document structural and functional change have been improving. In addition to subjective assessment of the optic disc and RNFL by clinical examination or photograph review objective methods including confocal scanning laser ophthalmoscopy, scanning laser polarimetry and optical coherence tomography are available to provide documentation of the optic disc and RNFL with sophisticated statistical analyses for glaucoma management. In addition to standard automated perimetry, selective perimetric techniques such as short wavelength automated perimetry (SWAP) and frequency doubling perimetry are now available to detect and monitor glaucomatous visual field changes.

Naturally, the ability to detect structural and functional change in glaucoma will vary depending on which structural and functional techniques are used. Other factors, including how glaucomatous change is defined, and the severity of disease will also affect the ability to detect glaucomatous change. This brief overview will summarize what we know about the temporal relationship between structural and functional change in glaucoma and how this information can be used in clinical practice. This review will focus on the limited number of well-

designed longitudinal studies (randomized clinical trials and observational cohort studies) that measured structural and functional change over time in order to answer the question: Is structural change usually detectable before functional change in glaucoma? This review will also briefly highlight study design issues that may explain differences in results across studies so that clinicians can better apply the information to their specific clinical populations.

RANDOMIZED CLINICAL TRIALS

In the past, most randomized clinical trials of glaucoma therapy relied on the reduction of IOP as the primary study endpoint. The studies that did not rely solely on IOP reduction, most often examined the progression of visual field loss (e.g. the Advanced Glaucoma Intervention Study,⁵ and Collaborative Initial Glaucoma Treatment Study⁶) and did not include an independent measure of optic disc structure as a primary study endpoint. More recently three randomized clinical trials (Ocular Hypertension Treatment Study (OHTS),⁷ Early Manifest Glaucoma Study (EMGT),⁸ and the European Glaucoma Prevention Study (EGPS)⁹ have included assessment of the optic disc along with visual field testing as primary endpoints for open angle glaucoma. These well-designed studies provide important information on the temporal relationship between structural and functional change in early glaucoma (Tables 1 and 2).

The OHTS and EGPS evaluated whether ocular hypotensive treatment delayed or prevented the development of glaucoma in participants with ocular hypertension. The OHTS, a National Eye Institute multi-center randomized clinical trial of 1636 ocular hypertensive patients, found that topical ocular hypotensive medication was effective in delaying and/or preventing the onset of POAG.¹⁰ In contrast to the OHTS, the EGPS a multi-center randomized, double-masked, placebo controlled study of 1,077 ocular hypertensives found that neither the degree of IOP-lowering nor the rate of progression to POAG was statistically different between the dorzolamide treated and placebo groups.¹¹

Table 1: Study design features of the OHTS, EGPS and EMGT

	OHTS ¹⁰	EGPS ¹¹	EMGT ¹⁶
Stage of disease at study entry	Ocular hypertensives: No sign of structural or functional damage	Ocular hypertensives: No sign of structural or functional damage	Early glaucoma: Reproducible field damage at baseline (99% had optic disc pathology at baseline)
Normal tension/exfoliation included	No/No	No/Yes 1.6% of study population	Yes/Yes 10% of study population
Structural change definition	Stereophotography “clinically significant optic disc deterioration attributed to POAG”	Stereophotography visually recognizable narrowing of the neuroretinal rim not attributable to photographic artifacts	Flicker chronoscopy and side-by-side comparisons of fundus photographs
Structural change graders	Masked graders from Optic disk reading center	Masked graders	Masked graders
Required repeatability of structural change	Yes	No	Suspected or definite changes confirmed using a second set of photographs
Frequency of photography	Annually	Annually	At 3 and 6 months, then every 6 months
Functional change definition	Humphrey field Analyzer: GHT or CPSD outside normal limits	Humphrey field Analyzer or Octopus: 1. 3 or more adjacent points that change > 5 dB from baseline, OR 2. 2 or more adjacent points that change >10 dB from baseline, OR 3. A difference of 10 dB or more across the nasal horizontal meridian in at least 2 adjacent points	Humphrey field Analyzer: the pattern deviation based glaucoma change probability maps with the same 3 changing test points (not necessarily contiguous)
Required repeatability of functional change	Confirmed on 3 consecutive exams with the same index and location	Repeatable in the same locations in 3 consecutive exams	3 exact test point locations confirmed on 3 consecutive exams
Frequency of VF Testing	Every 6 months	Every 6 months	Every 3 months

Although these studies came to different conclusions regarding the effect ocular hypertensive treatment on the development of glaucoma, both studies reported a substantial proportion of eyes with either structural or functional change as the first sign of glaucoma. Specifically, the OHTS¹⁰ and EGPS¹¹ showed that, in many eyes, repeatable structural defects were the first sign of glaucoma (55% and 40% respectively), whereas, in some eyes, functional defects were the first sign of progressive change (35% and 60%, respectively). A very small proportion of eyes (10% in the OHTS and 0% in the EGPS) showed structural

and functional change at the same time. It should be noted that the definition of the study endpoints of the OHTS and EGPS were similar (but not identical),¹² with both using masked independent assessment of stereophotography and repeatable visual field change confirmed by an endpoint committee (Table 1). In addition, both studies reported good reproducibility in the assessment of the stereophotographs.¹³⁻¹⁵

The EMGT reported that in early glaucoma patients, treatment was effective in reducing glaucomatous progression.¹⁶ EMGT compared the development of optic disk

Table 3: Detectable structural and functional change in selected observational cohort studies

		<i>Chauhan</i> ³⁰	<i>Kamal</i> ²⁷	<i>Artes</i> ³¹	<i>Strouthidis</i> ²⁵	<i>Girkin</i> ³⁷
Patients	Diagnosis	OAG	OHT	OAG	OHT	OAG
	N (eyes)	77	164	84	198	47
	Length of follow-up	5.5 years median	16-21 months	7.4 years median (range 2 to 9)	2 to 7 years	2 to 9 years
Structural assessment	Test Used	HRT	HRT	HRT	HRT	Stereophotography
	Progression criteria	TCA	Cup and rim change greater than variability	TCA (3 criteria levels)	Rim area regression (3 criteria levels)	Qualitative assessment
Functional assessment	Test Used	SAP	SAP	SAP HRP	SAP	SAP SWAP
	Progression Criteria	Glaucoma change probability	AGIS score change from 0 to > 1	Pattern deviation (3 criteria levels)	Pointwise linear regression (3 criteria levels)	AGIS score clinical scoring system
Event or rate based		Event	Event	Event and rate	Rate	Event
Type of change	Structural only	40%	29%	17% to 42%*	9% to 21%*	13% to 32%*^
	Functional only	4%	5%	17% to 42%*	15% to 20%*	0% to 6%*^
	Structural and functional	29%	8%	4% to 19%*	3% to 12%*	15% to 34%*^
	No progression	27%	59%	58% to 83%*	46% to 73%*	47% to 53%*^

*Criteria dependent, ^Calculated from reported results, OAG—open angle glaucoma, OHT—ocular hypertension, HRT—Heidelberg retina tomograph, TCA—Topographic change analysis, SAP—Standard automated perimetry, HRP—High pass resolution perimetry, SWAP—Short wavelength automated perimetry, AGIS—Advanced glaucoma intervention study

Analysis), and only 3 (4%) showed change only on SAP. Table 3 summarizes the results of selected observational cohort studies. In general, regardless of the type of structural or functional test used, these studies suggest that the first sign of glaucomatous change can be either structural or functional. Differences between these studies can be explained at least in part by differences in the criteria used to define glaucomatous progression. For example, several studies have shown that various algorithms used in clinical trials for identifying glaucomatous visual field progression identify different proportions of patients with progressive visual field loss.^{23,38,39}

A number of well-designed studies explicitly assess the effect of applying different stringency criteria for defining structural and functional progression in the same study population. Artes and Chauhan³¹ compared SAP, high pass resolution perimetry and HRT topographic change analysis in glaucoma patients utilizing three criteria of change (least conservative, intermediate and conservative) for each test. Regardless of the criteria, they found rather limited agreement

between SAP, high pass resolution perimetry and HRT for detecting change after an average of 7 years of follow-up and concluded that these indicators of structural and functional change provide “largely independent measures of progression”. Specifically, among the 60 patients classified as progressing using the least conservative criteria by at least one test, only 6 (10%) met the criteria for all 3 tests. Similarly, using the most conservative criteria, only 2 of the 27 (7%) progressing eyes showed progression on all 3 tests. Strouthidis et al.²⁵ compared rates of rim area and SAP sensitivity change over time in 198 ocular hypertensive patients and found that, depending on the stringency of the criteria, between 8% and 21% of eyes had documented rim area change, and another 15 to 20% had documented change in visual field sensitivity. Only 3 to 12% had both documented rim area and visual field sensitivity change. The authors conclude that “The results indicate that, in patients with ocular hypertension, monitoring of both VF and optic disc is necessary, as agreement between optic disc and VF progression is the exception rather than the rule.”

In summary, using a variety of diagnostic tests and definitions of progression from observational cohort studies provide evidence that in some eyes (13 to 42%), glaucomatous structural change is detected first, while in other eyes (4 to 42%) functional change is the first sign of glaucoma.^{23-28,30,31,35,37} Moreover, these studies consistently show that in fewer eyes (3 to 34%), structural and functional changes are detected at the same time.

DISCUSSION

There are many possible explanations for why in some eyes, structural change is detected first, whereas in others, functional change is detected first (See Hood and Kardon²⁹ for an excellent discussion of this issue). First, the ability to detect structural and functional damage depends on the instrument and parameters used to detect it. Since we cannot measure retinal ganglion cell function directly, we must rely on surrogates such as structural and functional testing. For example, visual function tests are designed to indirectly assess ganglion cell dysfunction. In some eyes, these psychophysical changes can be identified before cell death or before an anatomical structural change can be detected. It is also likely that in some eyes, structural changes can be detectable before visual sensitivity loss in areas of the visual field where redundancy of ganglion cells is high. Currently, there is no consensus on the best test or criteria for detecting glaucomatous change.² Moreover, the definition of progression in clinical studies and clinical practice is determined by balancing the magnitude of detectable change (signal) desired, with the variability of its detection (noise). If one tries to detect the earliest sign of change, it may be difficult to identify reproducibly and may lead to false positives; a larger change may be more reproducibly detected. Balancing these considerations to detect progression in an individual patient may be different from identifying small differences in the average course of disease in a group of patients in a clinical study.² Finally, as the reproducibility of tests varies by individual, type of test, and stage of disease, the test with the lowest variability (structural or functional) may reveal the first sign of glaucomatous change for a particular individual patient.^{29,31}

Which Technique to Use?

Techniques to monitor structural and functional change are improving. Based on the evidence from a limited number of studies available, there is no one structural or functional test or analysis technique that clearly outperforms the others in the detection of progression.^{2,40,41} (See Anderson et al² for a discussion of test criteria important for the detection of progression). A recent American Academy of Ophthalmology Ophthalmic Technology Assessment Report reviewed imaging instruments for detection of glaucoma and its progression and concluded that “Based on studies that have compared the

various available technologies directly, there is no single imaging device that outperforms the others in distinguishing patients with glaucoma from controls.⁴⁰ Sakata et al⁴¹ recently reviewed the evidence for selective perimetry in glaucoma management and concluded that “...visual dysfunction in eyes with early glaucoma varies significantly between individuals and no single technique is superior to the others in all patients.”

Techniques with lower measurement variability will be more likely to detect repeatable change. Each technique has advantages and disadvantages, and it is important for the clinician to understand the strengths and limitations of the technique used in their clinic.⁴¹⁻⁴⁴ Moreover, both structural and functional techniques should be used in conjunction with a careful clinical examination.

SUMMARY

Consistent evidence from clinical trials and observational cohort studies suggests that the first sign of glaucomatous change can be structural or functional. This is true in studies of ocular hypertensive patients and patients with early to moderate glaucoma using a variety of techniques and definitions of glaucomatous change. Based on current evidence, there is no one structural or functional technique that outperforms the others in detecting glaucomatous progression. Therefore, monitoring both structural and functional change in conjunction with a thorough clinical examination is essential for proper management of glaucoma patients.

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